Citation:

Hirsch S, Sanchez H, Albala C, de la Maza MP, Barrera G, Leiva L, Bunout D. Colon cancer in Chile before and after the start of the flour fortification program with folic acid. *European Journal of Gastroenterology & Hepatology*. 2009; 21: 436-439.

PubMed ID: 19190501

Study Design:

Trend Study

Class:

D - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To compare the rates of hospital discharges owing to colon cancer in Chile before (1992 to 1996) and after (2001 to 2004) mandatory fortification with 220 mcg folic acid per 100 g wheat flour.

Inclusion Criteria:

- Cancer or cardiovascular hospital discharge in Chile in from 1992 to 1996 or from 2001 to 2004
- Treating physician completed the discharge form (required for all discharges)
- Age 45 to 79 years (not explicitly stated in the article, but displayed in Table one)
- The Institute of Nutrition and Food Technology's ethics committee approved the research.

Exclusion Criteria:

- No explicit exclusion criteria were described
- Discharges for reasons other than cancer and cardiovascular disease
- Discharges before 1992, in 1994 or 1995, 1997 to 2001 or after 2004
- Age less than 45 or more than 79 years.

Description of Study Protocol:

Recruitment

Study did not involve recruitment. It was a population-based study of hospital discharge records.

Design

Hospital discharge rates for cancer were compared between periods before (1992 to 1996) and

after (2001 to 2004) mandatory folic acid fortification of wheat flour.

Statistical Analysis

- Standard error of the log rate ratios to derive confidence intervals (CI), and to test significant difference were calculated
- All statistical analyses were carried out using STATA 7.0.

Data Collection Summary:

Timing of Measurements

Hospital discharge records from 1992, 1993 and 1996 (pre-folic acid fortification) and 2002 to 2004 (post-fortification) were examined.

Dependent Variables

- Colorectal, breast and gastric cancer
- Ischemic, hypertensive and cerebrovascular diseases.

Independent Variables

Pre- vs. post-mandatory folic acid fortification of wheat flour (1992, 1993 and 1996 vs. 2002 to 2004).

Control Variables

Age (45 to 64 years; 65 to 79 years).

Description of Actual Data Sample:

- *Age:* 45 to 79 years
- *Location:* Chile.

Summary of Results:

Disease Group	Pre-fortification Rate per 100,000			Post-fortification Rate per 100,000			Rate Ratio	99% CI
	1992	1993	1996	2002	2003	2004		
Age 45 to 64 years								
Stroke	188.7	188.7	193.6	189.8	191.1	182.3	0.99	1.04 to 0.98
Hypertension	150.4	140.0	119.2	120.0	114.5	110.5	0.84	0.90 to 0.84
Ischemic heart disease	196.4	206.5	217.3	294.3	295.9	296.5	1.43	1.49 to 1.42

Breast cancer	71.4	62.4	69.3	135.7	145.4	141.9	2.08	2.24 to 2.07
Gastric cancer	63.3	57.1	54.5	56.0	57.0	60.6	0.99	1.09 to 0.99
Colon cancer	24.4	21.6	24.5	56.1	60.8	67.3	2.61	2.93 to 2.58
Age 65 to 79 years								
Stroke	771.5	822.0	828.6	875.1	860.8	834.4	1.06	1.10 to 1.06
Hypertension	407.0	400.1	381.3	358.9	350.1	334.5	0.88	0.93 to 0.87
Ischemic heart disease	579.6	633.9	671.4	778.1	812.6	805.2	1.27	1.33 to 1.27
Breast cancer	89.3	82.1	93.9	161.1	176.9	167.6	1.90	2.12 to 1.88
Gastric cancer	169.8	163.9	174.3	192.8	208.6	195.5	1.17	1.28 to 1.17
Colon cancer	62.7	65.8	78.4	178.9	208.0	214.5	2.90	3.25 to 2.86

- Among patients age 45 to 64 years:
  - Hospital discharges for colon cancer, breast cancer and ischemic heart disease increased significantly from pre- to post-fortification
  - Hospital discharges for hypertension decreased significantly
  - Rates for stroke and gastric cancer did not change
- Among patients age 65 to 79 years:
  - Hospital discharges for all diseases except hypertension increased significantly from pre- to post-fortification
  - Discharges for hypertension decreased significantly
- Rate ratios were highest for colon cancer in both age groups.

Other Findings

Mortality trends for all three cancers were similar to the discharge trends, but were not significant.

Author Conclusion:

- A temporal relationship between folic acid fortification and colorectal cancer hospital discharge rates was found; one explanation is that the rate changes were due to folate overload
- The observation for colorectal cancer is consistent with increased incidence of the disease observed post-fortification in the US and Canada
- The observation counters cohort and case-control studies in which inverse associations between plasma folate levels and colon adenomas or colorectal cancer
- The increased discharge rates for breast cancer may be due to an early detection program

that was launched in 2000.

Reviewer Comments:

- *The authors noted the following competing explanations:*
  - *Early detection programs for breast cancer (launched in 2000) may account for its increased hospital discharge rates*
  - *Colon and breast cancer discharge rates may both have increased due to rising incidence of factors such as obesity, low intakes of fiber and calcium and high intakes of fat and meat*
  - *Chile does not maintain a cancer registry. Therefore, hospital discharge data are a proxy for disease incidence*
- *The authors provided minimal detail on patient characteristics from the years of interest, and were not clear on their statistical analyses; rate ratio point estimates were not located in the center of the 99% CIs. While this may be due to log transformations, it is unclear whether this is the case based on the brief methods section of the paper*
- *Factors other than mandatory folic acid fortification may explain changes in hospital discharge rates between the two time periods. The failure or inability to make statistical adjustments for potential confounders (e.g., changes in obesity prevalence) or to address potential history threats to internal validity (e.g., changes in the number of colorectal cancer screenings and early detection) weakens the overall conclusions that can be drawn from the analyses. Similarly, both fortification and discharge rates are population-level variables; causal links between fortification and disease within individuals cannot be inferred from the data because individual intake patterns are unknown (i.e., the ecological fallacy)*
- *An additional consideration is that cancer or cardiovascular events are commonly understood to be diseases that develop over a long period of time. It is unclear whether mandatory fortification, implemented in 2000, could account for more than two-fold increases in hospital discharge rates from the pre- to post-fortification periods.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	N/A
2.3.	Were health, demographics, and other characteristics of subjects described?	No
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	???
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	???
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	N/A
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	???
4.1.	Were follow-up methods described and the same for all groups?	N/A
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	N/A

4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	???
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	No
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	N/A

7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	N/A
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	No
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	???
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	???
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	No
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	No
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes